PATENT
Attorney Docket No. BNIT0003-PCT-US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Application of: | ) | |
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| Søren MOURITSEN et al. | ) | Group Art Unit: 1644 |
| | ) | |
| Application No.: 08/955,373 | ) | Examiner: Ronald B. SCHWADRON |
| | ) | |
| Filed: October 21, 1997 | ) | |
| | ) | |
| For: INDUCING ANTIBODY RESPONSE AGAINST SELF-PROTEINS WITH THE AID OF FOREIGN T-CELL EPITOPES | ) | Confirmation No.: 7254 |
| | ) | |

**Attention: Mail Stop Appeal Brief-Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**REPLY BRIEF UNDER BOARD RULE § 41.37**

In support of the Notice of Appeal filed March 15, 2012, and further to Board Rule 41.41, Appellant presents this Reply Brief responding to the Examiner's Answer issued October 29, 2012, addressing the final rejection of claims 102, 103, 105, and 111 mailed February 15, 2012. This Reply Brief is accompanied by payment of the $630.00 fee required under 37 C.F.R. §§ 1.17(c) and 41.20(b)(2).

If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to **Deposit Account 50-5338**, referencing **Docket No. BNIT0003-PCT-US**.

## I. Status Of Claims

Appellants/Applicants have filed a total of 112 claims during prosecution of this application. Claims 1-87 and 101 have been canceled. Claims 88–100, 104, 106–110, and 112 have been withdrawn from consideration as drawn to non-elected species. Claims 102, 103, 105, and 111 are pending and currently under final rejection. No claims are allowed.

Appellants hereby appeal the final rejection of claims 102, 103, 105, and 111. A listing of the claims on appeal is attached to the Appeal Brief filed June 11, 2012, as Appendix A, according to the provisions of 37 C.F.R. § 41.37(c)(1)(viii).

## II. Grounds of Rejection

The four grounds of rejection presented herein for review are set forth below.

A. Claims 102, 103, 105, and 111 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

B. Claim 102 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over International Publication No. WO 92/05192 A1 ("Russell-Jones"), in view of US Patent No. 5,716,596 ("Dean") and US Patent No. 5,969,109 ("Bona").

C. Claim 111 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Russell-Jones, in view of Dean and Bona as applied to claim 102, further in view of International Publication No. WO 93/05810 A1 ("Hellman") and US Patent No. 5,698,195 ("Le").

D. Claims 103 and 105 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Russell-Jones, in view of Dean and Bona as applied to claim 102, and further in view of US Patent Publication No. US 2003/0099634 A1 ("Vitiello").

## III. Argument

The Examiner's Answer mailed October 29, 2012, brings no further insight to bear on the substance of Appellants' complaint.[1] The Examiner has again failed to accord proper weight to three separate Rule 1.132 Declarations filed by three different scientists working in the relevant technical field, each declaring under oath that the disputed claim language was not indefinite to a person of ordinary skill in the art. The Examiner also continues to improperly read additional limitations into the claims in an attempt to support his position. Moreover, the Examiner now objects to the consideration of what supplementary materials that were in fact published with a reference he himself recently cited against Appellants. Ignoring the USPTO's clear direction encouraging its Examiners and Applicants to constructively address outstanding issues in a timely manner, the Examiner at this late stage apparently blames Appellants for failing timely to advance prosecution to a close.

Even though the Examiner essentially relies on old arguments already addressed in the previously filed Appeal Brief, Appellants respond to certain aspects of the Examiner's arguments in more detail below.

### A. Response to the Rule 1.132 Declarations

Claims 102, 103, 105, and 111 have been rejected as allegedly indefinite under 35 U.S.C. § 112, second paragraph, for recitation of the phrase "the secondary structure and tertiary structure of the self-protein is preserved to a large extent". Examiner's Answer, item (1)(A), page 3. In an effort to rebut the Examiner's position, three separate Rule 1.132 Declarations signed under oath by three different scientists working in the relevant technical field were submitted during prosecution,

1 In fact, the Examiner does nothing more than copy and paste circular arguments from prior Office Actions, as illustrated by the presence of the same typographical errors throughout. *See, e.g.*, Examiner's Answer, item (1)(A), page 4 (stating "it is unclear if this term encompasses changes at the physical/chemical level (egg. crystal structured) or simply functional changes (egg. still immunogenic antigen as evidenced by antibody binding by antibodies specific for unmodified antigen)")(emphasis added).

each of which concluded that the meaning of the disputed claim language was definite to a person of ordinary skill in the art. *See* Appeal Brief filed June 11, 2012 ("Appeal Brief"), pages 13 and 18-24.

Nevertheless, the Examiner maintains that the three declarants "cannot agree as to what the phrases 'essential preservation of overall tertiary structure' or 'essentially preserve the secondary structure and tertiary structure' mean or encompass." Examiner's Answer, item (2)(A), page 11. Appellants believe that both phrases are definite, as demonstrated throughout the prosecution history. Yet the Examiner continues to apply the wrong legal standard to evaluate definiteness of claim language, and fails to consider the fact that the Declarations were filed years apart,[2] so that each Declarant assessed the meaning of the disputed claim term in the context of different claim language pending at the time each Declaration was filed. Certainly nothing stated in any of the three separate Declarations contradicts any other Declarant's assertions and conclusions.

Appellants reiterate that the acceptability of claim language under 35 U.S.C. §112, **¶2**, depends on whether one of ordinary skill in the art would understand what is claimed, when the claims are read in light of the specification. MPEP §2173.02 (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)). Despite differences in the claim language and the text of the Declarations, the prosecution file history shows that not one, not two, **but three separate persons of ordinary skill in the art** understood what is claimed. Note also that the definitions offered in each Declaration are entirely consistent with the language of the specification. MPEP §2173.02 (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)).

Moreover, the implication that the Declarations would not be relevant because "none of said declarations address the newly added limitation of the claim that the secondary and tertiary structure

2 The declarations filed include: (i) the Declaration of Professor Sven Frøkjaer, Ph.D., accompanying a Preliminary Amendment filed August 19, 1998; (ii) the Declaration of Dr. Paul Travers, accompanying a Response to Final Rejection filed October 9, 2000; and (iii) the Declaration of Alain Delcayre under 37 C.F.R. § 1.132 , accompanying the Amendment and Reply filed November 24, 2010.

is 'preserved to a large extent'[,]" is nonsensical. Final Action of February 15, 2012, item 4, page 3; and Examiner's Answer, item (2)(A), pages 11-12.

Claim 102 remains rejected as allegedly indefinite for reciting ". . . such that the secondary and tertiary structure of the self protein is preserved to a large extent[.]" Final Action of February 15, 2012, item 4, page 2. Previous versions of claim 102 reciting "…such that the secondary and tertiary structure of the self-protein *is essentially preserved*" were pending for much of the application's pendency, but were rejected on the same grounds, based on identical arguments. *See, e.g.*, Office Action of February 17, 2011, item 7, page 3. Appellants note that claim 102 was amended to its present form after the third and final Declaration was filed. That amendment changed the phrase 'is essentially preserved' to 'preserved to a large extent', *following the Examiner's own suggestion to adopt language taken directly from the specification* in order to address a written description rejection.

In a telephone interview conducted April 27, 2011 (*see, e.g.*, Amendment and Reply to Office Action filed June 17, 2011, at Section IV.A., page 9), Examiner Schwadron indicated that, in his view, *either* formulation of claim 102 raised similar issues 35 U.S.C. § 112, ¶2 for alleged indefiniteness. The Examiner's objection to the Declarations for [explicitly] failing to address the newly added limitation was raised specifically to the Travers Declaration (Final Action, item 4, page 3, stating "[re]garding the first Travers Declaration, said declaration addresses the phrase 'essentially preserve the overall tertiary structure' wherein said phrase is not currently recited in the claims under consideration") and generally to all three Declarations (Final Action, item 4, page 3, stating "none of said declarations address the newly added limitation that the secondary and tertiary structure is 'preserved to a large extent'"). The Examiner should not be permitted to disregard all three Declarations simply because Appellants amended the claims as he suggested in order to overcome a different ground of rejection.

Furthermore, Appellants understand both limitations "essentially preserved" and "to a large extent" to have the same meaning in the context of the claims and maintain that both terms would be clearly understood by a person of skill in the art reading the claims in light of the specification. The claim is functionally defined and that is the relevant limitation to the scope of the claim. The Examiner has no valid basis to disregard the previously submitted Declarations regarding definiteness simply because one term in the claims not used in the specification was substituted for an equivalent term actually used in the specification. Accordingly, the Examiner's objection regarding the Declarations is not valid or persuasive, and therefore should be disregarded.

Appellants thus respectfully maintain the position that the pending claims are definite in accord with 35 U.S.C. § 112, ¶2 and should be allowed.

**B. The Examiner improperly attempts to read additional limitations into the claims**

In an effort to overcome the Examiner's rejection of the pending claims as allegedly obvious under 35 U.S.C. §103(a), Appellants have argued that the claimed invention has unexpected properties not present in the prior art. However, the Examiner alleged that evidence of those unexpected properties was not commensurate in scope with the claimed invention because the pending claims encompass methods of treating humans while the experiments described in the specification were performed in mice.

Despite the fact that efficacy data in humans is not required to support patentability—particularly in cases where the supporting data was obtained using a well-accepted experimental model, as in the present application—Appellants submitted a Rule 1.132 Declaration by Dr. Fatema Legrand presenting the results of a human clinical trial using the claimed methods in an effort to overcome the obviousness rejection. *See, e.g.*, Declaration of Dr. Fatema Legrand, accompanying Amendment and Reply filed June 17, 2011 (the "Legrand Declaration"); *see also* Appeal Brief, pages

32-35. The Examiner responded by alleging that the experiments described in the Legrand Declaration were not "commensurate in scope with the claimed invention" and lacked nexus with the claimed invention because the recombinant HER2 used in those experiments was administered as MVA-BN-HER2, a recombinant vaccinia virus vector expressing the modified self-protein HER-2. Examiner's Answer, item (2)(B), pages 15-16. The Examiner apparently believes that the pending claims are limited to administration of protein antigens and do not encompass administration of protein antigens by delivery of a viral vector encoding one or more protein antigens.

Citing the Mandl et al. reference from 2011[3] discussed in more detail below, the Examiner further noted that the reference "disclose[s] that the MVA-BN-HER2 vector induces immune responses that are not seen upon vaccination with protein antigen and wherein said responses are critical to the results obtained when said vaccinia vector is administered[.]" Final Action, item 8, page 9. The Examiner then concluded that "the results obtained in the Legrand Declaration clearly depend on use of the MVA-BN-HER2 recombinant vaccinia vaccine vector wherein said vector is not the claimed invention or even an invention disclosed in the specification." Final Action, item 8, page 9.

Thus, the Examiner continues to mischaracterize the pending claims and improperly attempts to read at least two new limitations into the claims, the first requiring use of an MVA-BN® vector encoding a HER-2 analogue, the second apparently requiring induction of specific T-cell responses and anti-tumor efficacy. This objection must fail, because the pending claims recite a method of inducing autoantibodies against a self-protein in a subject, *i.e.*, against a particular self-protein antigen, not a method of inducing specific T-cell responses for treating cancer in a patient.

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3 S.J. Mandl et al., "Immunotherapy with MVA-BN®-HER2 induces HER-2-specific Th1 immunity and alters the intratumoral balance of effector and regulatory T cells," *Cancer Immunol. Immunother.* 61:19-29 (2012), published online August 7, 2011.

Furthermore, pending claim 102 *does not limit the 'administering' step to administration of a particular composition, formulation or route of delivery*, but simply recites "*administering to the subject an analog of the self-protein made by molecular biological means*[.]" As one of ordinary skill in the art would understand, the phrase 'an analog of the self-protein made by molecular biological means' encompasses both a recombinant self-protein analogue and a recombinant viral vector comprising a gene encoding that same self-protein analogue. Administration of recombinant self-protein analogues in either form was within the level of ordinary skill in the art at the time of filing, and as the Examiner must know, the specification "need not disclose what is well-known . . . and preferably omits that which is well-known" to those skilled in the art. MPEP § 2164.05(a) (internal citations omitted).

Finally, despite the Examiner's insistence that certain types of immune responses induced by administration of a self-protein analog (*e.g.*, HER-2) according to the present claims encoded by a recombinant vaccinia vector (*e.g.*, MVA-BN®-HER-2) but not by vaccination with a recombinant self-protein alone (*e.g.*, modified HER-2 protein), "are critical to the results obtained", the plain language of the claim recites only "such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein." Both the Legrand Declaration and Mandl et al. present data clearly showing that administration of both (1) a recombinant self-protein analog encoded by a recombinant vaccinia vector and (2) a recombinant self-protein analog according to the present claims induced HER-2-specific autoantibodies, and that is all the claims require. *See, e.g.*, Legrand Declaration, paragraph 15, Figure 1, page 7; and Mandl et al., Supplementary Figure 1.

Notwithstanding the Examiner's insistence to the contrary, Appellants respectfully assert that efficacy data in humans is not required to support patentability. Moreover, the evidence presented in the Legrand Declaration is commensurate in scope and has nexus with the pending

claims. Appellants therefore respectfully assert that the pending claims are not obvious under 35 U.S.C. § 103(a), and should be allowed.

### C. The Mandl Reference

Appellants maintain that the claimed invention has unexpected properties not present in the prior art and therefore is not obvious under 35 U.S.C. § 103(a), and submitted the Legrand Declaration in support of that position. Late in prosecution the Examiner relied on a reference by Mandl et al. (S. Mandl et al., "Immunotherapy with MVA-BN®-HER2 induces HER-2-specific Th1 immunity and alters the intratumoral balance of effector and regulatory T cells," *Cancer Immunol. Immunother.* 61:19-29 (2012)) to allege that the results presented in the Legrand Declaration "clearly depend on use of the MVA-BN-HER2 recombinant vaccinia vaccine vector" and therefore were not commensurate in scope and lacked nexus with the claimed invention. Final Office Action of February 15, 2012, item 8, page 9; and Examiner's Answer, item (2)(B), pages 15-17.

To rebut the Examiner's argument, Appellants pointed out that the pending claims only require that "administering to the subject an analog of the self-protein made by molecular biological means" in a quantity sufficient that the self-protein analog "induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein[.]" Appellants further noted that the supplementary material published with the Mandl et al. article clearly showed that treatment with the MVA-BN-HER2 construct in the tumor model used induced anti-HER2 antibodies—all that is required by the pending claims.

Because the copy of Mandl et al. provided by the Examiner did not include the electronic supplementary material—despite the fact that the front page of that reference clearly states that "[t]he online version of this article . . . contains supplementary material, which is available to authorized users"—Appellants submitted a complete copy of the reference with the Appeal Brief

filed June 11, 2012. Appeal Brief, Section X (Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)).

The Examiner now objects to the "newly submitted supplemental materials from Mandl et al. (**which were not previously of record and were submitted with the instant Brief**)" and furthermore maintains that "**the newly submitted supplemental materials from Mandl et al. disclose data that is not germane to the claimed invention**." Examiner's Answer, item (2)(B), page 22-23 (emphases original).

For reasons set forth above and in the previously-filed Appeal Brief, Appellants reiterate that the data disclosed in Mandl et al. is "germane to the claimed invention[.]" The Examiner cannot object to submission of the Supplementary Material from Mandl et al. simply because he failed to review the complete reference before he cited it.

Accordingly, the evidence presented in Mandl et al. is commensurate in scope and has nexus with the pending claims. Appellants therefore respectfully assert that the pending claims are not obvious under 35 U.S.C. § 103(a), and should be allowed.

**D. Grounds of Rejection to be Reviewed on Appeal**

Finally, Appellants' Appeal Brief noted that the present application has been pending before the same Examiner for more than fourteen years. Appeal Brief, Section I (Real Party-In-Interest), page 3. Appellants also pointed out that BN ImmunoTherapeutics, Inc., the current real-party-in-interest, acquired all right, title and interest in the claimed invention and assumed responsibility for prosecution of the current application less than four years ago, on February 20, 2009. *Id.* Furthermore, once the patent prosecution was taken over by Appellants, in order to bring the prosecution to a close, the claims were significantly revised to capture the disclosed invention and more clearly articulate the relevant limitations.

Nevertheless, the Examiner dismissed Appellants' assertion out-of-hand, responding tersely that "the instant application received a Final Rejection in May of 2000, after which appellants could have filed an Appeal Brief at any time." Examiner's Answer, item (1), page 3.

As a practical matter, the Examiner's response is simply not true, because Appellants assumed responsibility for prosecution of this application less than four years ago. Moreover, appeal of a Final Rejection to the Patent Trial and Appeal Board is a last recourse taken only when prosecution has reached an impasse.

After assuming control of prosecution, Appellants substantially revised the claims to address numerous issues raised throughout the prosecution file history and to more closely reflect the patentable subject matter disclosed in the specification. During the multiple rounds of prosecution that followed, Appellants interviewed the Examiner in order to clarify any remaining concerns and continued to revise the claim language in an effort to bring prosecution to a close. Despite Appellants' good faith efforts, however, the Examiner simply continued to recycle the same rejections, making the same circular arguments over and over and over again and delaying prosecution by filing two Notices of Non-Compliant Amendment contrary to the Office's guidance for Examiners.

## IV. Conclusion

For at least the reasons given above, pending claims 102, 103, 105, and 111 are allowable. Appellants respectfully ask the Patent Trial and Appeal Board to reconsider and reverse the outstanding rejections and pass this application through to allowance.

In the event that the United States Patent & Trademark Office ("USPTO") determines that other relief is required to obtain entry of this Reply Brief, Appellants hereby respectfully request such relief. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, kindly charge such fees to **Deposit Account 50-5338**, referencing Docket No. **BNIT0003-PCT-US**. However, the Commissioner is not authorized to charge the Issue Fee to the Deposit Account.

Respectfully submitted,

Dated: December 20, 2012

By: /David C. Hoffman/

David C. Hoffman, Ph.D., J.D.
Reg. No. 59,821
BN ImmunoTherapeutics, Inc.
2425 Garcia Avenue
Mountain View, CA 94043-1106
Phone: (650) 681-4780
E-mail: David.Hoffman@bn-it.com